FILE 'CAPLUS' ENTERED AT 09:51:49 ON 02 MAR 2001

=> S TUMOR SUPPRESSOR

215099 TUMOR
26552 SUPPRESSOR
L1 13287 TUMOR SUPPRESSOR
(TUMOR(W)SUPPRESSOR)

=> S HBOP;S MBOB;S HZAC;S MZAC;S CAMP

L2 1 HBOP

L3 2 MBOB

L4 1 HZAC

L5 1 MZAC

L6 66755 CAMP

=> S L2,L3,L4,L5

L7 4 (L2 OR L3 OR L4 OR L5)

=> D 1-4 CBIB ABS

L7 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2001 ACS
1998:492645 Document No. 129:212315 ***hZAC*** encodes a zinc finger protein with antiproliferative properties and maps to a chromosomal region frequently lost in cancer. Varrault, A.; Ciani, E.; Apiou, F.; Bilanges, B.; Hoffmann, A.; Pantaloni, C.; Bockaert, J.; Spengler, D.; Journot, L. (Centre National de la Recherche Scientifique, UPR 9023, Montpellier, F-34094, Fr.). Proc. Natl. Acad. Sci. U. S. A., 95(15), 8835-8840 (English) 1998. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.

AB We previously reported the identification of ***mZac*** , a novel mouse zinc finger protein that shared with p53 the ability to regulate concomitantly apoptosis and cell cycle progression. We describe here the isolation, chromosomal localization, and functional in vitro characterization of its human homolog. ***HZAC*** is a widely expressed zinc finger protein that reveals transactivation and DNA-binding activity. ***HZAC*** inhibits tumor cell growth through induction of apoptotic cell death and G1 arrest. Thus ***hZAC*** , like its mouse counterpart, displays antiproliferative properties through pathways known to be central to the activity of p53. We mapped ***hZAC*** on chromosome 6q24-q25, a region frequently deleted in many solid tumors. Indeed, allelic loss at 6q24-q25 has been shown in breast and ovary cancers, melanomas, astrocytomas, and renal cell carcinomas. Furthermore, Abdollahi et al. [Abdollahi, A., Godwin, A. K., Miller, P. D., Getts, L. A., Schultz, D. C., Tagushi, T., Testa, J. R. & Hamilton, T. C. (1997) Cancer Res. 57, 2029-2034] recently isolated ZAC through its loss of expression in a surface epithelial ovary tumor model and accordingly named it Lot for "lost on transformation.". In view of these observations, the functional properties we report here provide further arguments to consider ***hZAC*** as a tumor suppressor gene candidate.

L7 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2001 ACS
1997:189967 Document No. 126:212214 Significance of Borane Tuning in Titanium-Catalyzed Borylation Chemistry. Motry, Douglas H.; Brazil, Aimee G.; Smith, Milton R., III (Department of Chemistry, Michigan State University, East Lansing, MI, 48824, USA). J. Am. Chem. Soc., 119(11), 2743-2744 (English) 1997. CODEN: JACSAT. ISSN: 0002-7863. OTHER SOURCES: CASREACT 126:212214. Publisher: American Chemical Society.

GI

/ Structure 1 in file .gra /

AB The olefin complex, Cp*2Ti(.eta.2-CH2:CH2) (1), catalyzes the dehydrogenative borylation reaction between ethylene and benzo-1,3,2-diazaborolane (***HBOp***), to yield the vinylboronate amide CH2:C(H)BOp, I. In contrast to the analogous catalytic reaction between ethylene and catecholborane (HBcat), the selectivity for the stoichiometric reaction is preserved under catalytic conditions. The stoichiometric reaction between 1 and HBPOp yields Cp*2Ti(.eta.2-CH2:C(H)BOp) (3). The rate for borylation of the ethylene ligand in 1 by ***HBOp*** is considerably slower than the reaction for HBCat which yields Cp*2Ti(.eta.2-CH2:C(H)BCat) (2). While the equil. between 2 + CH2:CH2 and 1 + CH2:C(H)BCat is essentially thermoneutral at room temp. (Keq = 1.2(2), .DELTA.G.degree.reaction = 0.09(1) kcal/mol), the analogous equil. between 3 + CH2:CH2 and 1 + CH:C(H)BOp favors 1 (Keq .gtoreq. 1200, .DELTA.G.degree.reaction .ltoreq. -4.1 kcal/mol). Also, displacement of the vinyl boronate amide ligand in 3 by ethylene is rapid (even at -80.degree.) when compared to the reaction between ethylene and 2, which requires several days to reach equil. at room temp. Thus, the thermodn. and kinetic parameters favor regeneration of the active catalyst (1) when ***HBOp*** is employed as the borane reagent. Preliminary results indicate that ***HBOp*** has catalytic viability in other titanocene derived systems where borane-promoted catalyst decompn. is obsd. for HBCat.

L7 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2001 ACS
1994:318310 Document No. 120:318310 Molecular cloning of gene for MboI restriction-modification system of Moraxella bovis. Ueno, Takatsugu; Ito, Hiroyuki; Kotani, Hiroichi; Nakajima, Kazuo (Takara Shuzo Co, Japan). Jpn. Kokai Tokkyo Koho JP 05276943 A2 19931026 Heisei, 11 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 1993-16828 19930108. PRIORITY: JP 1992-46366 19920203.
AB An open reading frame contg. genes mboA, ***mboB*** , and mboC of Moraxella bovis is cloned and sequenced. The product of gene mboA is MboI modification enzyme. The upstream region of gene mboA is also cloned. Prepn. of MboI restriction endonuclease and MboI modification enzyme by expression of the genes in Escherichia coli was also shown.

L7 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2001 ACS
1993:510313 Document No. 119:110313 Gene structure and expression of the MboI restriction - modification system. Ueno, Takashi; Ito, Hiroyuki; Kimizuka, Fusao; Kotani, Hirokazu; Nakajima, Kazuo (Bioprod. Dev. Cent., Takara Shuzo Co., Ltd., Otsu, 520-21, Japan). Nucleic Acids Res., 21(10), 2309-13 (English) 1993. CODEN: NARHAD. ISSN: 0305-1048.
AB The genes from Moraxella bovis encoding the MboI restriction-modification system were cloned and expressed in Escherichia coli. Three open reading frames were found in the sequence contg. the genes. These genes, which the authors named mboA, ***mboB*** , and mboC, had the same orientation in the genome. Genes mboA and mboC encoded MboI methyltransferases (named M.MboA and M.MboC) with 294 and 273 amino acid residues, resp. The ***mboB*** gene coded for MboI restriction endonuclease (R.MboI) with 280 amino acid residues. Recombinant E.coli-MBOI, which contained the whole MboI system, overproduced R.MboI. R.MboI activity from E.coli-MBOI was 480-fold that of M. bovis. The amino acid sequences deduced from these genes were compared with those of other restriction-modification systems. The protein sequences of the MboI system had 38-49% homol. with those of the DpnII system.

=> S L1 AND L7

L8 1 L1 AND L7

=> S L1 AND L6

L9 89 L1 AND L6

=> S L1(6A)L6

L10 13 L1(6A)L6

=> S L10 NOT L7

L11 13 L10 NOT L7

=> D 1-13 CBIB ABS

L11 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2001 ACS
2001:113812 Schwann cell proliferative responses to cAMP and Nf1 are mediated by cyclin D1. Kim, Haesun A.; Ratner, Nancy; Roberts, Thomas M.; Stiles, Charles D. (Departments of Microbiology and Molecular Genetics, Harvard Medical School and the Dana-Farber Cancer Institute, Boston, MA, 02115, USA). J. Neurosci., 21(4), 1110-1116 (English) 2001. CODEN: JNRSDS. ISSN: 0270-6474. Publisher: Society for Neuroscience.

AB In most mammalian cells, the cAMP-dependent protein kinase A pathway promotes growth arrest and cell differentiation. However in Schwann cells, the reverse is true. Elevated levels of cAMP function as the cofactor to a broad range of mitogenic cues in culture and in animals. Previous studies have suggested that cAMP acts at an early point in the Schwann cell mitogenic response, perhaps by stimulating the expression of growth factor receptors. We show here that cAMP acts downstream rather than upstream of growth factor receptor expression. The essential function(s) of cAMP is exerted as Schwann cells progress through the G1 phase of the cell cycle. Ectopic expression studies using an inducible retroviral vector show that the G1 phase requirement for cAMP can be alleviated by a single protein, cyclin D1. We show, in addn., that at least one function of the Nf1 ***tumor*** ***suppressor*** is to antagonize the accumulation of ***cAMP*** and the expression of cyclin D1 in Schwann cells. Thus a G1 phase-specific protein, cyclin D1, accounts for two salient features of Schwann cell growth control: the promitotic response to cAMP and the antimitotic response to the Nf1 tumor suppressor.

L11 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2001 ACS
2000:447099 Document No. 133:204374 p53 recruitment of CREB binding protein mediated through phosphorylated CREB: a novel pathway of tumor suppressor regulation. Giebler, Holli A.; Lemasson, Isabelle; Nyborg, Jennifer K. (Department of Biochemistry and Molecular Biology, Colorado State University, Fort Collins, CO, 80523-1870, USA). Mol. Cell. Biol., 20(13), 4849-4858 (English) 2000. CODEN: MCEBD4. ISSN: 0270-7306. Publisher: American Society for Microbiology.

AB CREB binding protein (CBP) is a 270-kDa nuclear protein required for activated transcription of a large no. of cellular genes. Although CBP was originally discovered through its interaction with phosphorylated CREB (pCREB), it is utilized by a multitude of cellular transcription factors and viral oncoproteins. Both CREB and the tumor suppressor p53 have been shown to directly interact with the KIX domain of CBP. Although coactivator competition is an emerging theme in transcriptional regulation, we have made the fortuitous observation that protein kinase A-phosphorylated CREB strongly enhances p53 assocn. with KIX. Phosphorylated CREB also facilitates interaction of a p53 mutant, defective for KIX binding, indicating that CREB functions in a novel way to bridge p53 and the coactivator. This is accomplished through direct interaction between the bZIP domain of CREB and the amino terminus of p53; a protein-protein interaction that is also detected in vivo. Consistent with our biochem. observations, we show that stimulation of the intracellular cAMP (cAMP) pathway, which leads to CREB phosphorylation, strongly enhances both the transcriptional activation and apoptotic properties of p53. We propose that phosphorylated CREB mediates recruitment of CBP to p53-responsive promoters through direct interaction with p53. These observations provide evidence for a novel pathway that integrates cAMP signaling and p53 transcriptional activity.

L11 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2001 ACS
2000:212288 Document No. 133:133320 8-Br-cAMP up-regulates antioncogene expression in human retinoblastoma HXO-Rb44 cells. Deng, Xinguo; Guo, Xirang; Wu, Jinglan; Tian, Xiaoli; Pang, Guangren; Ma, Fengxia (Henan Inst. Ophthalmology, Zhengzhou, 450003, Peop. Rep. China). Yanke Yanjiu, 18(1), 1-3 (English) 2000. CODEN: YAYAFH. ISSN: 1003-0808. Publisher: Henansheng Yanke Yanjiuso.

AB Objective It is known that 8-Br-cAMP is one of selective binding site analogs for cAMP RII.alpha. to affect cell growth through regulation of gene expression. The p16, p21wafl, p53 and Rb are antioncogenes which affect cell growth through control of cell cycle. The aim of this study is to investigate the 8-Br-cAMP effect on the expression of antioncogenes in human HXO-Rb44 cells. Methods Cultured HXO-Rb44 cells in RPMI-1640 medium were divided into two aliquots. 8-Br-cAMP (2 x 10-5 mol/L) was added into one aliquot for 24 h as the exptl. group (EG). After 24 h, the cell aliquot without 8-Br-cAMP as the control group (CG). After 24 h, the cell suspension was dropped onto the nitrocellulose membrane. The mRNA of p16, p21 wafl, wild type (w) p53, mutant type (m) p53 and Rb were used resp.

with biotin-labeled cDNA probes by intact cell RNA dot blot. The immunoreactivity (IR) of P16, P21wafl, P Rb, PCNA, cdk2 and cdk4 were detected resp. with specific monoclonal antibodies on dot blot. Results The mRNA dot blot signals of mp53 and protein dot blot of cdk2-IR, cdk4-IR and PCNA-IR in EG were weaker than those in CG ($P < 0.05$.apprx.0.01). While, the mRNA signals of p16, p21wafl, wp53 and Rb in EG were stronger than those in CG ($P < 0.05$.apprx.0.01). The intensity of each protein dot blot was consistent with that of their RNA dot blot (except for wP53-IR and mP53-IR not to be done). Conclusions (1) 8-Br-cAMP could up-regulate expression of antioncogenes including p16, p21wafl, wp53, Rb, and protein expression of P16, P21wafl and PRb. (2) 8-Br-cAMP could down-regulate mp53 gene expression and protein expression of cdk2, cdk4 and PCNA. The results suggest that 8-Br-cAMP could inhibit human HXO-Rb44 cell growth through interfering related gene expression of cell cycle.

L11 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2001 ACS
2000:150213 Document No. 133:3090 The effect of 8-Br-cAMP on expression of antioncogenes in human retinoblastoma HXO-Rb44 cells in vitro. Deng, Xin-guo; Guo, Xue; Wu, Jing-lan; Guo, Xi-rang; Pang, Guang-ren; Tian, Xiao-li (Henan Inst. Ophthalmology, Zhengzhou, 450003, Peop. Rep. China). Jiepou Xuebao, 31(1), 61-64 (Chinese) 2000. CODEN: CPHPA5. ISSN: 0529-1356. Publisher: Zhongguo Jiepou Xuehui.

AB Objective: To study 8-Br-cAMP effect on cell growth and antioncogene expression in human retinoblastoma HXO-Rb44 cells. Methods: The p16INK4 mRNA, p21WAF1 mRNA, w (wild type)p53 mRNA, m (mutant type)p53 mRNA and Rb mRNA were detected by in situ hybridization and RNA dot blot technique. The PCNA, p16, p21WAF1, pRb, cdk2 and cdk4 proteins were detected by immunohistochem. and protein dot blot technique. Results: The signals of p21WAF1 mRNA, p16INK4 mRNA, wp53 mRNA, mp53 mRNA and Rb mRNA were localized in the cytoplasm of HXO-Rb44 cells. The p16-IR, p21WAF1-IR and pRb-IR were predominantly localized in the nuclei. In the dot blot the relative scanning value of p16INK4 mRNA, p21WAF1 mRNA, wp53 mRNA, Rb mRNA and p16-IR, p21WAF1-IR, pRb-IR of the exptl. groups (EG, treated with 8-Br-cAMP) was higher than that in resp. control groups (CG, treated with no 8-Br-cAMP), $P < 0.05$-0.01. However, the scanning value of the mp53 mRNA, PCNA-IR, cdk2-IR and cdk4-IR of EG was lower than that in resp. control groups, $P < 0.05$-0.01. Conclusions: (1)8-Br-cAMP could inhibit human HXo-Rb44 cell growth and proliferation. (2)8-Br-cAMP may up-regulate antioncogene expression, including mRNA expression of p16INK4, p21WAF1, wp53 and Rb and protein expression of p16, p21WAF1 and pRb. (3)8-Br-cAMP may down-regulate expression of mp53 mRNA, PCNA-IR, cdk2-IR and cdk4-IR expression. (4) The results suggest that 8-Br-cAMP may decrease human HXO-Rb44 cell growth via inhibition of cell cycle progressing related gene expression.

L11 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2001 ACS
1999:33337 Document No. 130:219039 ICER-II.gamma. is a ***tumor*** ***suppressor*** that mediates the antiproliferative activity of ***cAMP*** . Razavi, Reza; Ramos, Juan C.; Yehia, Ghassan; Schlotter, Florence; Molina, Carlos A. (Department of Obstetrics and Gynecology, New Jersey Medical School, Newark, NJ, 07103, USA). Oncogene, 17(23), 3015-3019 (English) 1998. CODEN: ONCNES. ISSN: 0950-9232. Publisher: Stockton Press.

AB The second messenger cAMP inhibits the proliferation of most cell types. The nuclear response of cAMP is mediated by transcription factors like the cAMP-Responsive Element Modulator (CREM) gene. One of the products of the CREM gene, the transcriptional repressor Inducible cAMP Early Repressor-II.gamma. (ICER-II.gamma.), is induced by cAMP. ICER-II.gamma. blocks cells at the G2/M boundary of the cell cycle. Here we show that ICER-II.gamma. dramatically inhibits the growth and DNA synthesis of mouse pituitary tumor cells and human choriocarcinoma cells. This alteration in cell growth is coupled with reduced ability of these cells to grow in an anchorage-independent manner and to form tumors in mice. These data demonstrate that ICER-II.gamma. is a tumor suppressor gene product mediating the antiproliferative activity of cAMP.

L11 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2001 ACS
1998:550239 Document No. 129:286067 Ultrastructural aspects of cAMP and p53-mediated apoptosis in normal and ras-transformed granulosa cells. Amsterdam, Abraham; Breckwoldt, Maren; Dantes, Ada; Natarajagounder, Selvaraj; Aharoni, Dorit (Department of Molecular Cell Biology, The Weizmann Institute of Science, Rehovot, Israel). Cell Death Reprod. Physiol., [Proc. Int. Symp.], Meeting Date 1996, 93-102. Editor(s): Tilly, Jonathan L.; Strauss, Jerome F., III. Springer: New York, N. Y. (English) 1997. CODEN: 66NTA2.

AB A review, with 34 refs., on apoptosis in normal and ras-transformed granulosa cells. Included were discussions on the control of apoptosis by multiple extracellular and intracellular signals; on tumor suppressor and survival genes as modulators of apoptosis; on intracellular compartmentalization of steroidogenic organelles which permit progesterone prodn. and apoptotic processes to coexist within the same cell; on actin cytoskeleton rearrangement during apoptosis; and on the presence of components controlling steroidogenesis in apoptotic blebs.

L11 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2001 ACS
1996:272998 Document No. 124:312958 Cross-talk between cAMP and p53-generated signals in induction of differentiation and apoptosis in steroidogenic granulosa cells. Amsterdam, Abraham; Keren-Tal, Iris; Aharoni, Dorit (Dep. Molecular Cell Biol., Weizmann Inst. Sci., Rehovot, Israel). Steroids, 61(4), 252-6 (English) 1996. CODEN: STEDAM. ISSN: 0039-128X.

AB A review, with 49 refs., on the cross-talk between cAMP and p53-generated signals in the regulation of the induction of steroidogenic granulosa cell differentiation and apoptosis. Compartmentalization of intracellular organelles during apoptosis may permit proteolysis without interfering with steroidogenesis, characteristic of the differentiated phenotype of the granulosa cell. Moreover, cytoskeletal rearrangement may serve as a barrier between these cellular activities.

L11 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2001 ACS
1995:639601 Document No. 123:80641 Endogenous gene expression of p53 and regulatory subunits of cyclic AMP-dependent protein kinase in ovarian cancer cells. Seo, Jin; Park, Woonmee; Kim, Jong Sik; Hwang, Eun Seong; Lee, Je-Ho; Hong, Seung Hwan (Inst. Mol. Biol. Genet., Seoul Natl. Univ., Seoul, 151-742, S. Korea). Tongmul Hakhoechi, 38(2), 204-11 (English) 1995. CODEN: TOHJAV. ISSN: 0440-2510.

AB In an effort to develop a new therapeutic strategy for human gene therapy of solid ovarian tumor, we studied the expression of the p53 tumor suppressor gene as well as regulatory subunits of cAMP (cAMP)-dependent protein kinase in human ovarian carcinoma cells. Four cell lines (2774, Caov-3, SK-OV-3 and OVCAR-3) were selected for the analyses. The p53 transcript and protein were detected only in the 2774 cell line by Northern and Western anal. In the relatively fast growing cell line, SK-Ov-3, the type 1 .alpha. regulatory subunit (RI.alpha.) of cAMP-dependent protein kinase was the highest among the four cell lines. The expression level of RII.beta. protein was low in the four cell lines examd. These results may point to a direction to select the target gene(s) to be employed for gene therapy to control the ovarian cancer.

L11 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2001 ACS
1995:550256 Document No. 122:282566 Involvement of p53 expression in cAMP-mediated apoptosis in immortalized granulosa cells. Keren-Tal, Iris; Suh, Byung-Sun; Dantes, Ada; Lindner, Serge; Oren, Moshe; Amsterdam, Abraham (Dep. Hormone Res., Weizmann Inst. Sci., Rehovot, 76100, Israel). Exp. Cell Res., 218(1), 283-95 (English) 1995. CODEN: ECREAL. ISSN: 0014-4827.

AB In the accompanying paper the authors described the induction of apoptosis by extended cAMP-mediated signals in primary granulosa cells and the redn. in this process in transformed cells expressing SV40 T antigen. In the present work, the authors examd. the effect of overexpression of either wild-type or mutant p53 on cAMP-mediated apoptosis in steroidogenic granulosa cell lines transfected with SV40 DNA together with the Ha-ras oncogene and a temp.-sensitive variant of p53, p53val135. In cell lines expressing low amts. of T antigen and high amts. of p53val135, growth arrest was induced by transferring the cells from 37.5.degree. to 32.degree., a temp. which allows the manifestation of the wild-type phenotype of p53 and the induction of the WAF1 gene. While nonstimulated cells showed only a very modest apoptotic process, rapid and massive apoptosis was evident in cells stimulated by forskolin at 32.degree.. The presence of serum could delay, but not abolish, this phenomenon. Progesterone prodn. in such cells treated with cAMP was significantly higher at 32.degree. than at 37.5.degree., suggesting that wild-type p53 can also enhance granulosa cell differentiation. Furthermore, at least at early stages, apoptosis is correlated with increased cell differentiation. In lines expressing high amts. of T antigen and low amts. of p53, neither an increase in cAMP-induced differentiation nor massive apoptosis was seen at 32.degree.. These findings demonstrate that wild-type p53 can cooperate with cAMP-generated signals in the induction of steroidogenesis and of programmed cell death in granulosa cells.

L11 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2001 ACS
1995:550255 Document No. 122:282688 cAMP-mediated signals as determinants for apoptosis in primary granulosa cells. Aharoni, Dorit; Dantes, Ada; Oren, Moshe; Amsterdam, Abraham (Dep. Hormone Res., Weizmann Inst. Sci., Rehovot, 76100, Israel). Exp. Cell Res., 218(1), 271-82 (English) 1995. CODEN: ECREAL. ISSN: 0014-4827.

AB Differentiation and luteinization of granulosa cells are induced by gonadotrophic hormones and other substances elevating intracellular levels of cAMP. The authors have investigated the correlation between the potency of these substances to enhance steroidogenesis and to induce apoptosis in primary granulosa cell cultures obtained from rat preovulatory follicles. The cAMP analog, 8-Br cAMP, induced apoptosis in >90% of the cell population within 15 h of incubation at 37.degree. in serum-free medium. The physiol. stimulants of these cells, FSH and LH, which caused a moderate cAMP response in these cells, followed by a desensitization period, increased progesterone prodn. by 4-fold with no apparent effect on cell death. In contrast, forskolin, a potent activator of adenylate cyclase, stimulated both the cAMP and steroidogenic response by an order of magnitude greater than the gonadotropin stimulation, concomitantly with a pronounced increase in cell death (25%). Moreover, blocking of the cellular phosphodiesterase activity in forskolin-stimulated cells by isobutylmethylxanthine (IBMX), which maintains high levels of intracellular cAMP, led to further enhancement of cell death following 40 h of incubation (50%). Basic FGF (bFGF) and gonadotropin-releasing hormone (GnRH), which stimulated steroidogenesis in these cells in a cAMP-independent manner, did not promote cell death. Moreover, costimulation of the cells with forskolin and bFGF led to a substantial decrease in the incidence of apoptosis relative to forskolin alone. To exam. whether the expression of tumor suppressor genes is involved in granulosa cell differentiation and apoptosis induced by cAMP, the authors examd. the effect of cAMP in SV40 transformed granulosa cells, in which T-antigen expression is expected to block the activity of p53 as well as of the retinoblastoma gene product (pRB) and its related proteins. Cultures of 3 different cell lines established by SV40 transformation demonstrated resistance to 8-Br-cAMP- or forskolin plus IBMX-induced apoptosis, in contrast to the severe apoptotic response in primary cells. The authors suggest that stimulation of primary granulosa cells by high levels of cAMP catalyzes programmed cell death, while stimulation of the cells by gonadotropic hormones, which result in a moderate cAMP response, followed by desensitization to further stimulation, can prolong the lifespan of the luteinized granulosa cells. Moreover, one or more ***tumor*** ***suppressor*** proteins may mediate the ***cAMP*** -generated signal leading to cell death.

L11 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2001 ACS
1995:423716 Document No. 122:184821 Signalling and chromatin fragmentation in thymocyte apoptosis. McConkey, David J.; Nicotera, Pierluigi; Orrenius, Sten (Division Toxicology, Institute Environmental Medicine, Stockholm, S-17177, Swed.). Immunol. Rev., 142, 343-63 (English) 1994. CODEN: IMRED2. ISSN: 0105-2896.

AB A review, with .apprx. 106 refs., discussing signaling mediators (e.g. calcium, p53 ***tumor*** ***suppressor*** , PKC, ***cAMP*** , and ceramide) in apoptosis, chromatin degrdn. in apoptosis, and the role of oxygen radicals.

L11 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2001 ACS
1994:576991 Document No. 121:176991 The regulation of apoptosis in thymocytes. McConkey, David J.; Jondal, Mikael; Orrenius, Sten (MD Anderson Cancer Center, University of Texas, Houston, TX, 77030, USA). Biochem. Soc. Trans., 22(3), 606-10 (English) 1994. CODEN: BCSTB5. ISSN: 0300-5127.

AB A review, with 66 refs., discussing mechanisms (calcium, ***cAMP*** , PKC, p53 ***tumor*** ***suppressor*** , Myc, and Nur77) that regulate apoptosis triggering, the involvement of cross-talk, and the programming of apoptosis sensitivity.

L11 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2001 ACS
1994:531136 Document No. 121:131136 Retroviral vector-mediated overexpression of the RII.beta. subunit of the cAMP-dependent protein kinase induces differentiation in human leukemia cells and reverts the transformed phenotype of mouse fibroblasts. Tortora, Giampaolo; Budillon, Alfredo; Yokozaki, Hiroshi; Clair, Timothy; Pepe, Stefano; Merlo, Girogio; Rohlff, Christian; Cho-Chung, Yoon Sang (Cell. Biol. Sect., Lab. Tumor Immunol. Biol., Bethesda, MD, 20892, USA). Cell Growth Differ., 5(7), 753-9 (English) 1994. CODEN: CGDIE7. ISSN: 1044-9523.

AB The authors have recently shown, using antisense strategy, that the RII.beta. regulatory subunit of cAMP-dependent protein kinase is essential for cAMP-induced growth inhibition and differentiation of HL-60 human leukemia cells. The authors constructed a retroviral vector for RII.beta. (MT-RII.beta.) by inserting human RII.beta. complementary DNA into the OT1521 retroviral vector plasmid that contains an internal mouse metallothionein-1 promoter and a neomycin resistance gene. The PA317 packaging cell line was then transfected with MT-RII.beta. retroviral vector. The infection with MT-RII.beta. and treatment with CdC12 brought about growth arrest in HL-60 human leukemia and Ki-ras-transformed NIH 3T3 clone DT cells in monolayer culture with no sign of toxicity. The growth inhibition correlated with the expression of RII.beta. and accompanied changes in cell morphol.; cells became flat, exhibiting enlarged cytoplasm. The growth of these cells in semisolid medium (anchorage-independent growth) was almost completely suppressed. In contrast, overexpression of the RI.alpha. subunit of protein kinase enhanced the cell proliferation in DT cells. The MT-RII.beta.-infected cells exhibited an increased sensitivity toward treatment with cAMP analogs, such as 8-Cl-cAMP and N6-benzyl-cAMP, as compared with the parental noninfected cells. In MT-RII.beta. HL-60 cells, N6- benzyl-cAMP treatment greatly enhanced the expression of monocytic surface markers. These results suggest that the RII.beta. cAMP receptor, by binding to its ligand, ***cAMP*** , acts as a ***tumor*** ***suppressor*** protein exerting growth inhibition, differentiation, and reverse transformation.

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=> E SPENGLER D/AU
=> S E3,E6,E7

             6 "SPENGLER D"/AU
            15 "SPENGLER DIETMAR"/AU
             1 "SPENGLER DIETMAR H"/AU
L12         22 ("SPENGLER D"/AU OR "SPENGLER DIETMAR"/AU OR "SPENGLER DIETMAR
               H"/AU)

=> E JOURNOT L/AU
=> S E3,E4

            11 "JOURNOT L"/AU
            26 "JOURNOT LAURENT"/AU
L13         37 ("JOURNOT L"/AU OR "JOURNOT LAURENT"/AU)

=> S L12,L13

L14         45 (L12 OR L13)

=> S L14 AND L1

L15          5 L14 AND L1

=> S L15 NOT (L7,L11)

L16          4 L15 NOT ((L7 OR L11))

=> D 1-4 CBIB ABS
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L16 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2001 ACS
1999:486711 Document No. 131:241237 Loss of expression of the candidate ***tumor*** ***suppressor*** gene ZAC in breast cancer cell lines and primary tumors. Bilanges, Benoit; Varrault, Annie; Basyuk, Eugenia; Rodriguez, Carmen; Mazumdar, Abhijit; Pantaloni, Colette; Bockaert, Joel; Theillet, Charles; ***Spengler, Dietmar*** ; ***Journot, Laurent*** (UPR 9023 CNRS, Mecanismes Moleculaires des Communications Cellulaires, CCIPE, Montpellier, 34094, Fr.). Oncogene, 18(27), 3979-3988 (English) 1999. CODEN: ONCNES. ISSN: 0950-9232. Publisher: Stockton Press.

AB Loss of chromosome 6q21-qter is the second most frequent loss of chromosomal material in sporadic breast neoplasms suggesting the presence of at least one ***tumor*** ***suppressor*** gene on 6q. The authors recently isolated a cDNA encoding a new zinc finger protein which the authors named ZAC according to its functional properties, namely induction of apoptosis and control of cell cycle progression. ZAC is expressed in normal mammary gland and maps to 6q24-q25, a recognized breast cancer hot spot on 6q. In the present report, the authors

investigated the possible inactivation of ZAC in breast cancer cell lines and primary tumors. The authors detected no mutation in ZAC coding region in a panel of 45 breast tumors with allelic imbalance of 6q24-q25. However, a survey of eight breast cancer cell lines showed a deeply reduced (three cell lines) or complete loss of (five cell lines) ZAC expression. Treatment of three of these cell lines with the methylation-interfering agent 5-azacytidine induced ZAC re-expression. In addn., Northern blot and RNase protection assay anal. of ZAC expression in 23 unselected primary breast tumors showed a reduced expression in several samples. Together with its functional properties and chromosomal localization, these findings substantiate ZAC as a good candidate for the ***tumor*** ***suppressor*** gene on 6q24-q25.

L16 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2001 ACS
1999:340306 Document No. 131:153872 Induction of the PAC1-R (PACAP-type I receptor) gene by p53 and Zac. Ciani, Elisabetta; Hoffmann, Anke; Schmidt, Peer; ***Journot, Laurent*** ; ***Spengler, Dietmar*** (Department of Molecular Neurobiology, Max Planck Institute of Psychiatry, Munich, D-80804, Germany). Mol. Brain Res., 69(2), 290-294 (English) 1999. CODEN: MBREE4. ISSN: 0169-328X. Publisher: Elsevier Science B.V..

AB Pituitary adenylate cyclase-activating polypeptides and PAC1-R are expressed during early embryogenesis and PACAP's neurotrophic action supports a role in neuronal development. In the adult brain PACAP functions as a neuroprotective factor that attenuates the neuronal damage resulting from various insults. The ***tumor*** ***suppressor*** gene p53 and the new zinc finger protein Zac regulate apoptosis and cell cycle arrest through unrelated pathways and both genes are up-regulated under cerebral ischemia. We report here that p53 and Zac induce expression of the PAC1-R gene. By this mechanism p53 and Zac could fine-tune the balance between death promoting and protective signals and may thus fulfill a dual role in ischemia.

L16 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2001 ACS
1999:69144 Document No. 130:279754 Induction of type I PACAP receptor expression by the new zinc finger protein Zac1 and p53. Hoffmann, Anke; Ciani, Elisabetta; Houssami, Souheir; Brabet, Philippe; ***Journot,*** *** Laurent*** ; ***Spengler, Dietmar*** (Max-Planck Institute of Psychiatry, Molecular Neurobiology and Neuropathology, Munich, 80804, Germany). Ann. N. Y. Acad. Sci., 865(VIP, PACAP, and Related Peptides), 49-58 (English) 1998. CODEN: ANYAA9. ISSN: 0077-8923. Publisher: New York Academy of Sciences.

AB We reported recently the cloning of the type I PACAP receptor by a functional expression cloning technique. Unexpectedly, we obsd. addnl. PACAP-pos. pools that turned out to encode the wild-type form of the ***tumor*** ***suppressor*** gene p53 and the novel zinc finger protein Zac1, which regulates apoptosis and cell cycle arrest. Both Zac1 and p53 caused, under transient or stably regulated expression, induction of the type I PACAP receptor by transcriptional mechanisms. Transactivation of the type I PACAP receptor gene by Zac1 and p53 points to a subtle balance between death promoting and protective mechanisms. The control of these processes is central to various physiol. conditions ranging from development to senescence, whereas dysregulation may lead to overt pathol. outcomes, notably cancer, immune deficiency syndromes, and neurodegenerative disorders.

L16 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2001 ACS
1998:210854 Document No. 128:279573 Nucleic acid molecules coding for ***tumor*** ***suppressor*** proteins Bopl/ZAC and their diagnostic and therapeutic uses. ***Spengler, Dietmar*** ; ***Journot,*** *** Laurent*** (Max-Planck-Gesellschaft zur Forderung der Wissenschaften E.V., Germany; Centre National de la Recherche Scientifique; Spengler, Dietmar; Journot, Laurent). PCT Int. Appl. WO 9813489 A1 19980402, 125 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1997-EP5198 19970922. PRIORITY: US 1996-718661 19960923.

AB Described are novel proteins having the biol. activity of a ***tumor*** ***suppressor*** protein and nucleic mols. coding for such proteins. Methods for the isolation of nucleic acid mols. encoding ***tumor*** ***suppressor*** proteins as well as nucleic acid mols. obtainable by said method are also provided. The novel expression cloning technique relies on the transcriptional induction of a gene coding for a G-protein coupled receptor which in its activated form stimulates the cAMP signaling pathway which in turn results in the induction of cAMP responsive gene. Structural anal. of Bopl demonstrated features compatible with a transcription factor composed of a N-terminal seven zinc-finger

DNA-binding domain and a C-terminal transactivation domain. The overall identity between murine Bopl, also called ZAC, and human ZAC coding sequences was 74.6% at the nucleotide level and 68.5% at the amino acid level. Bopl displays the ability to suppress tumor cell proliferation which could be demonstrated by the constitutive and induced expression of said protein in transfected tumor cells. Furthermore, Bopl is capable of inhibiting anchorage-independent growth, suppress tumor formation of transformed cells injected in nude mice, induces apoptosis resulting in inhibition of tumor cell growth, induces G1 arrest of the cell cycle, and acts as a nuclear transcription factor. Further, vectors comprising said nucleic mols. wherein the nucleic acid mols. are operatively linked to regulatory elements allowing expression in prokaryotic or eukaryotic host cells can be used for the prodn. of polypeptides encoded by said nucleic acid mols. which have ***tumor*** ***suppressor*** activity. Pharmaceutical and diagnostic compns. are provided comprising the nucleic acid mols. of the invention and/or comprising a nucleic acid mol. which is complementary to such a nucleic acid mol. Described are also compns. which comprise polypeptides encoded by the described nucleic acid mols. which have **tumor*** ***suppressor*** activity and/or an antibody specifically recognizing such polypeptides.

	L #	Hits	Search Text	DBs
1	L1	1299	TUMOR ADJ SUPPRESSOR	USPAT
2	L2	0	HBOP	USPAT
3	L3	1	HBOP?	USPAT
4	L4	3	MBOP?	USPAT
5	L5	4	HZAC	USPAT
6	L6	0	MZAC	USPAT
7	L7	9954	CAMP	USPAT
8	L8	119	L1 AND L7	USPAT
9	L9	0	L1 NEAR6 L7	USPAT
10	L10	0	L1 NEAR10 L7	USPAT
11	L11	8	L3 OR L4 OR L5	USPAT